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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/063,553	05/02/2002	Audrey Goddard	P3230R1C001-168	9988

30313 7590 07/26/2005

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

DATE MAILED: 07/26/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/063,553	GODDARD ET AL.	
	Examiner	Art Unit	
	Daniel Kolker	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 June 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *02 May 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date 6/2/05
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. The Art Unit location of your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Art Unit 1649.Applicant's remarks, amendments, and declarations filed 2 June 2005 have been entered in full. Applicant has cancelled claims 1 – 3 and added new claims 14 – 17. Claims 4 – 17 are pending and under examination.

3. The correction of inventorship under 37 CFR 1.48(b) is acknowledged.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Priority

5. On pp. 9 – 10 of the remarks, applicant indicates that the instantly-claimed sequence of SEQ ID NO:48 was first disclosed in provisional application 60/090688 filed 25 June 1998, and that the data relied on in part for the utility of the claimed polynucleotides were first disclosed on PCT/US00/23328. On p. 2 of the previous office action the examiner indicated that the instant application receives priority to 24 August 2000, the date the international application was filed. The effective priority date is maintained, as applicant agrees that the first enabling disclosure, including the results of the assay described herein as example 18, is the date the international application was filed.

Information Disclosure Statement

6. The information disclosure statement filed 2 June 2005 has been considered. The BLAST results indicate that applicants are aware of proteins with identity or homology to the one claimed herein. However the results cannot be considered because there is no alignment provided, nor is there an indication of the percent identity between the claimed sequence and the reference sequences. Applicant states on pp. 8 - 9 of the remarks that the newly-submitted documents include references to specific accession numbers and sequences. Applicant is advised that the BLAST results submitted appear to be a list of sequences which match, but do not provide either alignments or indications of how the sequences are related to the peptides to which the instantly-claimed antibodies bind. Therefore the examiner cannot determine if the sequence accession numbers submitted by applicant constitute prior art. Furthermore the

search results submitted appear to be the results are not publicly available documents. Applicant is directed to MPEP 609 and 37 CFR 1.97 and 1.98.

Withdrawn Rejections and Objections

7. The following rejections and objections made in the previous office action are withdrawn:

The objections to the specification. Applicant has provided a more descriptive title and has deleted browser-executable hyperlinks.

The rejection of claims 4 – 13 under 35 USC 112, first paragraph for failing to fully meet the requirements for biological deposits. Applicant's signed statement filed 2 June 2005 is sufficient to overcome the enablement rejection related to biological deposits.

The rejection of claims 4 – 13 under 35 USC 112, second paragraph, for being indefinite. Applicant has amended the claims to recite specific extracellular domains and has deleted recitations of the extracellular domain without the signal peptide.

Maintained Rejections and Objections

Claim Rejections - 35 USC §§ 101 and 112

8. Claims 4 – 17 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility.

The claims are drawn to polypeptides at least 95% identical to SEQ ID NO:48, also called PRO994, as well as chimeric proteins comprising same. The specification discloses, on pp. 140 – 144, the results of an assay in which certain cDNA molecules showed differential expression in tumor tissue versus control tissue. The results indicate that DNA58855-1422, which encodes PRO994 (see specification p. 15, paragraph 73) is more highly expressed in normal stomach than in stomach tumor, and is more highly expressed in rectum tumor than in normal rectum. The specification (p. 140, paragraph 530) asserts that a nucleic acid molecule differentially expressed in normal as compared to tumor cells of the same tissue is useful as a diagnostic to determine the presence or absence of a tumor. The specification also asserts that nucleic acids differentially expressed in tumors are useful as therapeutic targets for the treatment of tumors.

It is important to note that the instant claims are drawn to proteins, whereas the data presented in the specification are based on assays performed with nucleic acids.

On p. 10 of the remarks applicant refers to MPEP 2107.01 which provides discussion as to the utility guidelines. Applicant further cites *Juicy Whip v. Orange Bang* as providing support for the argument that utility should be found for the instant invention.

The *Juicy Whip* case is not relevant. In *Juicy Whip*, the PTO had made a rejection, and the lower court upheld the rejection under 35 USC 101 because the invention was designed to deceive consumers. The CAFC overturned the rejection because the invention itself was useful in that it allowed the vendor to clean the bowls less frequently. In the instant case, the PTO has not made a 101 rejection because of an intent to deceive, but rather because the invention itself has no utility.

The text from MPEP cited by applicant on page 11, first complete paragraph of the remarks is not relevant here. The text tells the examiner not to impose a rejection based on lack of utility if applicant's "assertion would be considered credible by a person of ordinary skill in the art". The instant claims have not been rejected for lack of a credible utility, but rather for lack of specific and substantial utility. Similarly, the text from MPEP 2107.02 III B cited in the middle of p. 8 of the remarks is also drawn to discussions of rejections under 35 USC 101 for assertions of an incredible utility, but the examiner has not made such a rejection herein.

The specification discloses that a 200 – 600 bp fragment of a nucleic acid which encodes PRO994 is more highly expressed in normal stomach than in stomach tumor, and is more highly expressed in rectum tumor than in normal rectum. Applicant appears to have concluded that differential expression of the nucleic acid automatically will result in a differential expression of the protein, which should be sufficient to impute utility to the protein (i.e. SEQ ID NO:48). But the art recognizes that mRNA expression level is not well correlated with protein expression level. See, for example, Haynes et al. (1998), Electrophoresis 19:1862-1871 (cited by applicant on IDS filed 2 June 2005), particularly p. 1863, which indicates that mRNA levels can vary up to 40-fold without a change in protein level. In summary, applicant's disclosure of a change in levels of a fragment of the nucleic acid encoding SEQ ID NO:48, wherein the levels are increased in some tumors and decreased in others, are not sufficient to make the protein encoded by the full-length nucleic acid useful.

On pp. 11 - 12 of the remarks, applicant argues that utility need not be proven, that a reasonable correlation between the evidence and the asserted utility is sufficient, and that the guidance provided in MPEP § 2107.02 VII indicates that the asserted utility should be accepted if it is more likely than not true. Applicant cites *In re Langer*, *In re Jolles*, *In re Irons*, *In re*

Sichert, *Raytheon v. Roper*, and *In re Oetiker* as supporting this argument. Applicant's arguments have been fully considered but are not persuasive.

In the instant case, applicant has asserted that the protein of SEQ ID NO:48 have utility because it can be used to diagnose cancer. On p. 140-144 of the specification there is a table which indicates that a small fragment of a nucleic acid which encodes SEQ ID NO:48 is more highly expressed in rectum tumor than in normal rectum (i.e. upregulated in rectum tumor), and expressed less in stomach tumor than in normal stomach (i.e. downregulated in stomach tumor). Since PRO994 expression *increases* in one tumor and *decreases* in another, its expression level cannot be considered as a marker for the presence or absence of a tumor. There is no correlation between the level of PRO994-encoding nucleic acid and the presence or absence of a tumor.

Since there is not a correlation between the level of PRO994-encoding nucleic acid and the presence of a tumor, there is no basis for the asserted use of the PRO994 protein or nucleic acid as a therapeutic target for treatment of the disease condition. Because the correlation between expression of the nucleic acid and the protein is poor, data as to the expression of nucleic acids do not bear on the utility of proteins. Clearly, further research and experimentation are required to find out whether SEQ ID NO:48 are useful as asserted, particularly as the nucleic acid sequence used was from an undisclosed portion of SEQ ID NO:47, and are not indicative of changes in the full-length protein SEQ ID NO:48.

In *In re Langer*, the court ruled the Patent Office cannot require clinical testing in humans to rebut a prima facie case for lack of utility. In the instant case, the Office has not made such a requirement. Furthermore the Langer court ruled that "Assuming that sufficient reason to question the statement of utility and its scope does exist, a rejection for lack of utility under § 101 will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the statement of utility and its scope as found in the specification are true." In the instant case there is in fact sufficient reason to question the statement of utility. The instantly-claimed proteins are not clearly useful as either diagnostics or therapeutics for cancer, because there is not evidence of a correlation between the expression level of the protein and the presence or absence of a tumor.

In *In re Jolles*, the issue was whether data from an art-recognized animal model could be considered predictive of results in humans. That is not an issue in the instant case, as the data presented on pp. 140 – 144 of the specification are from human tissue samples. If there were a

correlation between the expression level of SEQ ID NO:48 and the presence of cancer, there might be a patentable utility for the protein. However, since there is not evidence of such a correlation applicant's arguments do not seem to be on point.

The citation of *In re Irons* is also not relevant to the instant case. In *Irons*, evidence was submitted that indicated that the drug had been administered to 888 patients and that statistically significant results were obtained showing an improvement in arthritic conditions. In the instant case, no such evidence has been submitted. The only data of record are drawn to the nucleic acid, but the instant claims are drawn to protein. Furthermore, there is no evidence of record indicating a statistically significant result at either the nucleic acid or the protein level.

The *Sichert* court ruled that blind comparative studies of the claimed compositions, which showed that the compositions were effective in relieving lymphatic congestion (as narrowly defined), were sufficient to establish utility of said compositions under 35 USC § 101. In the instant case, applicant has not shown any such studies, and therefore because the fact pattern is sufficiently different the *Sichert* case is not germane.

In *Raytheon v. Roper*, utility was found by the Federal Circuit when a lack of utility had been found by a lower court. This was due not to the sufficiency of the evidence presented, but rather because the Federal Circuit ruled that the claims in question had been interpreted erroneously. In the instant case, there does not appear to be a question as to how the pending claims are being interpreted. Rather, utility is found to be lacking because there is not a correlation between SEQ ID NO:48 expression and the presence or absence of cancer.

It is not immediately apparent why applicant has cited *In re Oetiker* in arguments related to the utility under 35 USC § 101, as the *Oetiker* case dealt not with utility but with obviousness under 35 USC § 103. No claims have been rejected under § 103 in the instant case.

Applicant also cites *In re Brana*, wherein it was pointed out the PTO has the initial burden to offer evidence that one of ordinary skill would doubt the asserted utility. In fact, on p. 3 of the office action mailed 1 March 2005, the examiner quite clearly indicated that "changes in PR0994 expression, even if they are statistically significant, are at the level of nucleic acid, which is not necessarily correlated with protein expression or activity." No rebuttal evidence has been presented, therefore whether or not said evidence is reasonably indicative of the asserted utility cannot be evaluated. This argument is reiterated on p. 24 of the remarks and is deemed not persuasive for the same reasons: no rebuttal evidence drawn to the utility of the instantly-claimed protein has been presented.

In *Fujikawa v. Wattanasin*, the court ruled that test results need not absolutely prove the asserted utility. The examiner recognizes that this precedent holds, however in the instant case, there is not a correlation between the instantly-claimed product (i.e. the polypeptide with SEQ ID NO:48) and any disease or condition.

On p. 13 of the remarks, applicant cites *Cross v. Iizuka*. As applicant indicates, the *Cross* court ruled that in vitro tests could be predictive of in vivo results and if an appropriate in vitro test is used that may be sufficient to confer utility under 35 USC 101. However, as pointed out previously, the specification does not disclose the results of any tests, *in vitro* or *in vivo*, that support the utility of SEQ ID NO:48.

In summary, applicant's arguments that absolute proof is not necessary, and that a reasonable correlation between the evidence presented and the asserted utility should be sufficient to give utility to the claimed invention do not carry weight. This is because there is not evidence of a correlation between the presence or absence of SEQ ID NO:48 and cancer.

On p. 16 of the remarks, applicant refers to the declaration by Grimaldi (exhibit 1) in which the importance of the data in Example 18 are explained.

The declaration (exhibit 1) under 37 CFR 1.132 filed 2 June 2005 is insufficient to overcome the rejection of claims 4 - 17 based upon lack of utility as set forth in the last Office action because:

1) The declaration is not commensurate in scope with the claims. The claims are drawn to SEQ ID NO:48, which is a polypeptide encoded by SEQ ID NO:47. The specification (page 140, paragraph 530) indicates that oligonucleotide probes were designed to amplify a portion of the DNA. The declaration indicates (paragraph 6) that using PCR, relative expression levels were scored for the fragments analyzed. Clearly, what was analyzed was the expression level of a part of SEQ ID NO:47, not the entire sequence. Furthermore, the fragment which was analyzed is not identified either in the specification or the declaration. The data presented are narrow, in that they deal with a fragment of SEQ ID NO:47 200 – 600 bp in length. In contrast, the claims are drawn to a different invention, i.e. to full-length protein of SEQ ID NO:48 or fragments or variants thereof.

2) The data presented are subjective in nature and not objective. Paragraph 6 of the declaration indicates that expression levels were assigned one of three values: +,-, or +/-. There is no indication how the expression levels were scored, nor is there any indication of what differentiates either a + or – sample from an intermediate (+/-) sample. Additionally, there is no

indication that the data are repeatable, as the experiments seem to have been performed once on a single sample. Furthermore, because there is no indication that the differences observed are statistically significant, it appears likely that the variability seen is not significant and would be expected by random variation alone. This is corroborated by the fact that PRO994 is up-regulated in rectum tumor but down-regulated in stomach tumor. In paragraph 7 of the declaration, Dr. Grimaldi states that the nucleic acids are useful in detection of cancer. But clearly this is contradicted by the evidence in the specification, which shows that expression of the nucleic acid is not correlated with the presence of cancer. Applicant concludes that there is a two-fold difference in expression level (remarks, p. 16, final complete paragraph) but there are not sufficient facts in the record to support such a conclusion. The declaration states that a visible change on an ethidium bromide-stained agarose gel is sufficient to support the conclusion that a two-fold difference in cDNA expression. But this is not supported by sufficient facts, such as presentation of a standard curve which correlates expression level to staining intensity and corrects for length of nucleotide, as longer pieces of nucleic acid will have more ethidium bromide staining. It is noted that the literature cautions researchers from drawing conclusions based on small changes in transcript expression levels between normal and cancerous tissue. For example, as discussed above, Hu et al. (2003, Journal of Proteome Research 2:405-412) analyzed 2286 genes that showed a greater than I-fold difference in mean expression level between breast cancer samples and normal samples in a microarray (p. 408, middle of right column) and discovered that, for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a known role in the disease. However, among genes with a 10-fold or more change in expression level, there was a strong and significant correlation between expression level and a published role in the disease (see discussion section). Additionally, the reference by Tokunaga et al. (2000. J Exp Clin Cancer Res 19:375-381, cited on IDS filed 2 June 2005) teaches that qualitative analysis of gene expression in cancer tissue using RT-PCR is not sufficient, rather quantitative analysis must also be used. Additionally Tokunaga teaches that for clinical applications (i.e. the diagnostic utility of the instantly-claimed nucleic acid) much further research is needed (see final sentence of abstract). Finally, Chen et al. (2002. Molecular and Cellular Proteomics 1.4pp. 304-313, cited on IDS filed 2 June 2005) teach that of 165 nucleic acid-protein pairs examined, only a small subset showed a significant correlation

and that overall there is not a significant correlation between gene expression and protein expression in cancer.

3) The actual data were not submitted in the declaration, rather a description of how the data were scored was submitted. The magnitude of the differences cannot be evaluated because the data were not submitted.

On p. 17 of the remarks applicant refers to the length of the cDNA used, and concludes that because the cDNA products were not likely to be under-represented in a library they are reflective of changes in the tissue. These remarks are not on point, as the instant claims are drawn to protein not to cDNA. As pointed out in the preceding paragraphs, there is no evidence that the protein with SEQ ID NO:48 is over- or under-expressed in any tumor, and the art recognizes that protein levels cannot be easily predicted from nucleic acid expression levels.

On pp. 18 - 19 of the remarks applicant refers to Exhibit 2, a second declaration submitted by Dr. Grimaldi. The declaration (exhibit 2) under 37 CFR 1.132 filed 2 June 2005 is insufficient to overcome the rejection of claims 4 – 17 based upon lack of utility as set forth in the last Office action because:

The facts presented are not germane to the rejection at issue. In paragraph 5, Dr. Grimaldi asserts that there are often correlations between expression of nucleic acid and of protein. The specification discloses that there are certain changes in expression of an unspecified fragment of SEQ ID NO:47 in some forms of cancer. As mentioned above, the teachings of Hu et al. indicate that subtle differences in gene expression are to be interpreted with great caution, and Haynes et al. teach there is not a strong correlation between gene expression at the level of nucleic acid and at the level of protein. Since the present claims are drawn to the protein, and the only data provided are on a fragment of a nucleic acid sequence, the statements are not on point.

At pp. 19 – 20, Applicant presents a declaration by Dr. Polakis filed with the response under 37 CFR 1.132. In the declaration, Dr. Polakis states that the primary focus of the Tumor Antigen Project was to identify tumor cell markers useful as targets for cancer diagnostics and therapeutics. Dr. Polakis states that approximately 200 gene transcripts were identified that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Dr. Polakis states that antibodies to approximately 30 of the tumor antigen polypeptides have been developed and used to show that approximately 80% of the samples show correlation between increased mRNA levels and changes in polypeptide levels. Dr. Polakis

states that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide. Dr. Polakis characterizes the reports of instances where such a correlation does not exist as exceptions to the rule. This has been fully considered but is not found to be persuasive.

First, it is important to note that the instant specification discloses that the expression of a part of the nucleic acid encoding SEQ ID NO:48 is not correlated with cancer. It is increased in cancer in one tissue and decreased in another. Therefore, the declaration is insufficient to overcome the rejection of the claims under 35 USC 101. Furthermore, the declaration does not provide data such that the examiner can independently draw conclusions. Only Dr. Polakis' conclusions are provided in the declaration. The declaration is not on point to the claimed sequence as it does not state that these successes are in using cancer diagnostics with the instantly-claimed sequences. The evidentiary support to Dr. Polakis' statement that it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded polypeptide is not on point to the instantly-claimed protein. There is no evidence provided in the declaration that there is a correlation between mRNA levels and protein expression for SEQ ID NO:48. In fact, the references by Haynes and Chen cited above show that mRNA expression level is not well correlated with protein expression level. Furthermore, the text from applicant's exhibit 4, p. 453, cited by applicant on p. 20 of the remarks clearly indicates that other controls can act later in the pathway from RNA to protein.

Applicant also presents arguments from exhibits 5 – 8 in support of the arguments for utility. The arguments from exhibits 5 – 7 are concerned with the correlation between mRNA levels and protein levels. Exhibits 5 and 6 discuss regulation of genes in general but are not on point to the specific protein at issue here i.e. SEQ ID NO:48. Exhibit 7 is drawn to a specific protein, namely PSCA, but is not germane because the claims are not directed to either PSCA; they are drawn to antibodies which bind to a different, unrelated protein. The argument from exhibit 8 (Meric et al.) is that differences in gene expression between normal and cancer cells makes those genes targets for therapeutics. However in the instant case there is not evidence of a correlation between the expression of the fragment of SEQ ID NO:47 and the presence of cancer, so the sequence cannot reasonably be construed as a target for a therapeutic. In fact, the next sentence in the paragraph of Exhibit 8 cited by applicant is directly on point "Gene expression is quite complicated, however, and is also regulated at the level of mRNA stability, mRNA translation, and protein stability." Thus the paragrpah presented by applicant, taken in

its entirety, suggests that it is not proper to conclude that there are changes in protein level when changes in the mRNA level are observed.

On p. 22, applicant refers to the declaration submitted by Dr. Ashkenazi (exhibited 9). The declaration under 37 CFR 1.132 filed 2 June 2005 is insufficient to overcome the rejection of claims 4 – 17 based upon lack of utility as set forth in the last Office action because:

The Ashkenazi declaration filed under 37 CFR § 1.132 argues that, even when amplification of a gene in a tumor does not correlate with an increase in polypeptide expression, the absence of the gene product over-expression still provides significant information for cancer diagnosis and treatment. This has been fully considered but is not found to be persuasive. In the instant case, the data presented in the specification were from an RT-PCR assay, not a gene amplification assay. It is possible that utility might be found if a gene were found to be overexpressed at the nucleic acid level but not at the protein level, and the change in expression at the nucleic acid had predictive value as a diagnostic (i.e., if there were a statistically significant correlation between expression level the claimed sequence and the presence of cancer). However, in the instant case, the fragment of the nucleic acid with SEQ ID NO:47 has not been found to be correlated with cancer expression. Furthermore, there is no evidence as to whether the gene products (i.e. the polypeptide) are over-expressed or not. Considerable further research is required to determine such. Thus, the asserted utility is not substantial, as the claims are drawn to polypeptides and not to nucleic acid.

On p. 24, applicant argues that the asserted utilities are specific and substantial for the claimed proteins "because the PRO994 gene is differentially expressed in stomach tumors or rectum tumors". This is not on point, because the instant claims are drawn to proteins but the gene which applicant refers to is nucleic acid. For the reasons pointed out above, there is reason to doubt that changes seen in the nucleic acid level will be reflected in the protein, and applicant has not presented evidence that the protein levels are correlated with the presence or absence of cancer.

Applicant points out, in the paragraph from MPEP 2107.02 cited on page 24 of the remarks, that partial success is sufficient to demonstrate patentable utility. However in the instant case the only data presented are drawn to a patentably and biochemically distinct product, namely a portion of the nucleic acid of SEQ ID NO:47. The claims are drawn to the polypeptide of SEQ ID NO:48, and no data have been presented as to the utility of the peptide. Thus the remarks are not on point.

Applicant points out, in the paragraph from MPEP 2107.01 cited on page 26 of the remarks, that partial success is sufficient to demonstrate patentable utility and that if inventions are partially successful in achieving results, lack of utility rejections should not be made on the basis of wholly incredible utilities. But this text is excepted from MPEP 2107.01 (II), drawn to the discussion of rejections that are wholly inoperable and lack credible utility. In the instant case, the claims have not been rejected under 35 USC 101 for a lack of a credible utility, but rather for lack of a specific and substantial utility. Thus the remarks are not on point. Furthermore applicant has not shown that the instantly-claimed invention is even partially successful in achieving any result, and thus the remarks are not relevant.

Newly submitted claims are drawn to proteins at least 95% or 99% identical to SEQ ID NO:48, wherein the variant or fragment can be used to make an antibody, as well as chimeric molecules comprising same. For the reasons made of record in the previous office action and reiterated above, proteins 100% identical to SEQ ID NO:48 are not considered useful, and certainly proteins which are not identical to SEQ ID NO:48 are also not useful. Antibodies can be used to detect proteins. But since the requirement of new claims 14 – 17 is that the fragment or variant be capable of detecting SEQ ID NO:48, and there is no use for SEQ ID NO:48, there would be no use for the antibodies which could be raised against the variant. Applicant is directed to MPEP § 2107.01 (II), particularly the discussion of substantial utility. The text clearly states that methods "of assaying for or identifying a material that itself has no specific and/or substantial utility" are not useful. The same logic applies to products whose only use would be to detect or purify a product which is not useful.

Therefore the rejection of claims 4 – 17 under 35 USC 101 stands.

9. Claims 4 - 17 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Even if utility were found for PRO994 (SEQ ID NO:48), enablement would still not be commensurate in scope with claims 4 – 5, and 12 – 13 because the specification does not reasonably provide enablement for fragments or variants 95% or 99% identical to SEQ ID NO:48 which are more highly expressed in normal stomach tissue or rectum tumor compared to stomach tumor or normal rectum tissue, or for fragments or variants encoded by polynucleotides with said expression profile. The specification does not enable any person skilled in the art to

which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claims 4 – 5 and dependent claims 12 – 13 have been amended to recite that the polypeptide be more highly expressed in normal stomach or rectum tumor tissue than stomach tumor or normal rectum tumor respectively, and the claims further require that the protein be at least 95% (claims 4, 12 – 13) or 99% (claim 5) identical to SEQ ID NO:48. However, the instant specification does not provide any working examples of proteins which meet those limitations. There are no examples of any proteins which are expressed more according to this pattern. The only example of any product with such an expression pattern is a small fragment, 200 – 600 bp long, of SEQ ID NO:47, which is a nucleic acid. A skilled artisan would have to resort to an undue amount of experimentation to make and use the proteins as claimed. The specification does not provide guidance as to which regions of the protein are necessary for the fragments or variants to have the claimed expression pattern. The artisan would first have to identify those regions which are crucial for such an expression pattern in protein, if in fact there is one. Then the artisan would have to make variants, and test those variants for the expression pattern. Because the only data in the specification are drawn to nucleic acid, and there is reason to doubt that changes in expression of a small piece of nucleic acid are informative as to changes in the expression of the protein, and because there are no examples of any proteins which have the expression pattern, such experimentation would be undue.

On p. 29 of the remarks, applicant argues that amended claims are analogous to example 14 of the written description training materials. The examiner disagrees. First, it is important to note that the instant rejection is drawn to enablement, not written description and thus is not on point. Nonetheless, Example 14 of the training materials indicates that if a protein which is known to have a particular activity is disclosed, it would be inappropriate to make a rejection over claims to 95% variants having the same activity. Importantly, in the instant case, no activity has been disclosed for the claimed protein SEQ ID NO:48. Applicant has not presented evidence that SEQ ID NO:48 fulfills the expression pattern recited in claims 4 and 5. Therefore since the protein with 100% identity to SEQ ID NO:48 is not disclosed to have an activity (here, an expression pattern), Example 14 is not analogous.

On p. 30 of the remarks, applicant argues that the issuance of other patents with claims to variants of protein sequences wherein the applicants did not actually make the claimed variants provide a reason that the 112, first paragraph rejections should be withdrawn. The

examiner disagrees. As applicant notes, the issuance of other patents is not binding on the instant application, and since applicant has not shown how to make or use the claimed variants, the claims remain rejected under 35 USC 112.

11. Claims 4 – 5 and 12 – 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant cites *In re Kaslow*, *Vas-Cath Inc. v. Mahurkar*, and *Union Oil v. Atlantic Richfield Co.* as providing the basis for the determination of whether or not claims meet the description requirement of 35 USC 112, first paragraph. The examiner agrees.

Applicant argues on p. 32 of the remarks that the disclosure of a single polypeptide, that of SEQ ID NO:48, is sufficient to provide a description of those variants at least 95% or 99% identical thereto having the expression profile recited in claims 4 and 5. The examiner disagrees. The specification does not show which regions of SEQ ID NO:48 are required for the resulting variants or fragments to have the instantly-claimed activity. Applicant has not described a correlation between the structural elements and the recited activity. The specification discloses only the full-length protein (SEQ ID NO:48) and not any variants or fragments. There is no disclosure that the full-length protein has the claimed expression profile.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

Applicant again argues, on p. 33 of the remarks, that Example 14 of the written description guidelines is analogous to the instant claims. The examiner disagrees. Example 14 is drawn to variants at least 95% identical to a sequence, wherein the variants have the disclosed activity of the sequence. But in the instant case, there is no disclosure that SEQ ID NO:48 has the claimed expression profile. Therefore the situation is not analogous.

Therefore, polypeptides comprising the sequence of SEQ ID NO:48, but not the full breadth of the claims meet the written description provision of 35 U.S.C. § 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

Rejections and Objections Necessitated by Amendment

Claim Objections

12. Claims 14 and 15 are objected to because of the following informalities: They are drawn to non-elected subject matter. Part (d) of both claims recites "SEQ ID NO:74". The remainder of the instant claims are drawn to SEQ ID NO:48. Appropriate correction is required.

Claim Rejections - 35 USC § 112

13. Even if utility were found for PRO994 (SEQ ID NO:48) claims 4 – 17 would remain rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for extracellular domains at residues 32 – 49 or 111 – 190 of SEQ ID NO:48 (claims 4 – 17) or SEQ ID NO:74 (claims 14 – 15). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Figure 48 of the specification indicates the location of four transmembrane domains, but neither the figure nor the specification discloses which eegions of the protein are intracellular or extracellular. The protein has four transmembrane domains. If the N-terminal region of the protein is intracellular, then the regions between residues 32 – 49 and 111 – 190 are in fact extracellular. However if the N-terminal region is extracellular, then residues 1 – 9, 73 – 86, and 214 – 229 are extracellular. The specification does not disclose which regions are intracellular and which are extracellular, and thus a skilled artisan would not be able to make and use the claimed proteins, fragments, variants, and chimeric proteins comprising same with the assurance that the recited domains are extracellular.

Claims 14 and 15 recite SEQ ID NO:74 in part (d). Figure 74 of the specification discloses that SEQ ID NO:74 has a single transmembrane domain at residues 291 – 310. A skilled artisan could not make a variant of SEQ ID NO:74 with the assurance that the extracellular domains are from residues 32 – 49 and 111 – 190 because the specification does not disclose which end of SEQ ID NO:74 is intracellular and which end is extracellular. Furthermore sequences at least 95% identical to SEQ ID NO:74 cannot be used to generate antibodies that recognize SEQ ID NO:48. Those sequences would be expected to generate antibodies which bind to SEQ ID NO:74. A skilled artisan would recognize that antibodies bind to the polypeptides which serve as the antigens in raising them.

14. Claims 4 – 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 4 – 11 and 14 – 15 recite two specific extracellular domains, consisting of residues 32 – 49 and 111 – 190 of SEQ ID NO:48. Figure 48 of the specification indicates the location of four transmembrane domains, but neither the figure nor the specification discloses which eegions of the protein are intracellular or extracellular. The protein has four transmembrane domains. If the N-terminal region of the protein is intracellular, then the regions between residues 32 – 49 and 111 – 190 are in fact extracellular. However if the N-terminal region is extracellular, then residues 1 – 9, 73 – 86, and 214 – 229 are extracellular. Since there was not disclosure of which regions were intracellular or extraceullar in the specification, drawings, or claims as originally filed, identification of such regions is deemed to be new matter.

15. Claims 14 – 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

Claims 14 and 15 recite the limitation "wherein said isolated polypeptide or a fragment thereof can be used to generate an antibody". Applicant has not shown which regions of the peptide must be conserved in order to raise antibodies which can detect SEQ ID NO:48. There is not a description of the regions of the polypeptide or fragments thereof which have antigenic

activity sufficient to raise antibodies. Furthermore claims 14 and 15 are drawn to fragments at least 95% identical to SEQ ID NO:74, which can be used to raise antibodies against SEQ ID NO:48. Applicant has not demonstrated which regions of SEQ ID NO:74 could be used to raise antibodies that recognize SEQ ID NO:48.

Vas-Cath Inc. v. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Claims 16 and 17 depend from claim 14 and are rejected for the same reasons.

Conclusion

16. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel Kolker whose telephone number is (571) 272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Daniel E. Kolker, Ph.D.
July 20, 2005

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